REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made.

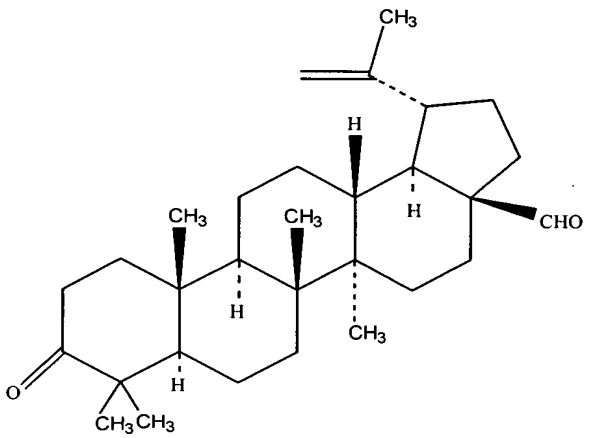
The rejection of claims 1-11 under 35 U.S.C. § 101 for lack an asserted utility is respectfully traversed. In particular, a utility for the compounds of claims 1-11 (i.e., diethers) is asserted at page 7, lines 15-16 of the specification, where it states: "[t]he compounds, diethers, and betulinol-antibody conjugates of the present invention can be used to treat patients suffering from cancer." Thus, applicants have asserted a specific and substantial utility that is credible in accordance with Utility Examination Guidelines, 66 Fed. Reg. 1092 (January 5, 2001) (see also the Declaration of Brij B. Saxena Under 37 CFR § 1.132, enclosed herewith and described below). Accordingly, the rejection of claims 1-11 under 35 U.S.C. § 101 is improper and should be withdrawn.

The rejection of claims 1-47 under 35 U.S.C. § 112, first paragraph, for lack of enablement is respectfully traversed.

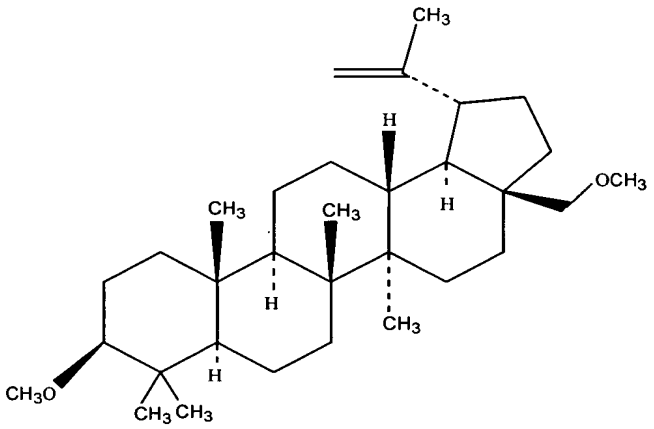
With respect to claims 1-11, it is the position of the U.S. Patent and Trademark Office ("PTO") that no activity or use for the compounds of claims 1-11 has been demonstrated and that since the claimed invention is not supported by an asserted utility, one skilled in the art would not know how to use the claimed invention.

As described above, a utility for the compounds of claims 1-11 (i.e., diethers) is asserted at page 7, lines 15-16 of the specification (i.e., to treat patients suffering from cancer).

In addition, as set forth in the enclosed Declaration of Brij B. Saxena Under 37 CFR § 1.132 ("Saxena Declaration"), the claimed diethers have been shown to be useful for treating patients suffering from cancer (Saxena Declaration ¶ 5). In particular, betulinol aldehyde



and a betulinol diether



were submitted to the National Cancer Institute for evaluation for anti-cancer activity (Saxena Declaration ¶ 6). The compounds were subjected to a 3-cell line panel consisting of NCI-H460 (lung), MCF7 (breast), and SF-268 (central nervous system). Id. This 3-cell line, one-dose assay has been in use the National Cancer institute for the evaluation of combinatorial libraries and has proven to be an effective pre-screen. Id.

In the 3-cell line, one dose assay, each cell line is inoculated and pre-incubated on a microtiter plate (Saxena Declaration ¶ 7). Test agents (e.g., betulinol aldehyde or betulinol diether) are then added at a single concentration and the culture incubated for 48 hours. Id. End point determinations are made with sulforhodamine B, a protein-binding dye. Id. Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Id. Compounds which reduce the growth of any one of the cell lines to 32% or less (negative numbers indicate cell kill) are active and are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range. Id.

Both betulinol aldehyde and the betulinol diether were found to exhibit anti-cancer activity by the National Cancer Institute's 3-cell line, one dose primary anti-cancer assay, as shown in Table 1, below (Saxena Declaration ¶ 8):

Table 1. Evaluation in the 3-cell line, one dose primary anti-cancer assay.

Sample	**Concentration**	**NCI-H460 (lung) – growth %**	**MCF7 (breast) – growth %**	**SF-268 (CNS) – growth %**	**Activity**
betulinol aldehyde	1×10^{-4} Molar	11	32	73	Active
betulinol dimethyl ether	1×10^{-4} Molar	20	3	-5	Active

In particular, betulinol aldehyde reduced the growth of the NCI-H460 (lung) and MCF7 (breast) cell lines to 32% or less. Id. The betulinol diether reduced the growth of the NCI-H460 (lung) and MCF7 (breast) cell lines to 20% or less. Id. Accordingly, betulinol diethers, as claimed in claims 1-11 of the above-identified application, can be used to treat patients suffering from cancer.

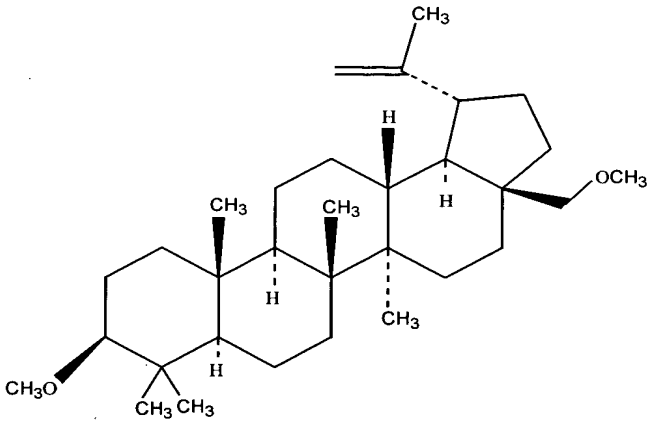
With respect to claims 12-47, which are drawn to peptide and antibody conjugates of betulinol and methods of preparing such conjugates, it is the PTO's position that there is no evidence that the peptide and antibody conjugates of betulinol will exhibit any particular activity.

In contrast, it has been demonstrated that betulinol (or derivatives thereof) exhibits anti-cancer activity, as shown in Example 4 at page 34, line 8, to page 35, line 10, of the present application. In particular, betulinol diacetate and betulonic aldehyde were both shown to exhibit high anti-carcinogenic activity in Example 4 (see, e.g., Specification at page 35, lines 6-7). In addition, betulinol aldehyde and betulinol diether were shown to exhibit anti-cancer activity, as described above (Saxena Declaration ¶¶ 6-8). Conjugating betulinol (or derivatives thereof) with peptides and antibodies merely targets the betulinol to a desired site (see Specification at page 28, line 27, to page 29, line 8). Thus, peptide and antibody conjugates of betulinol will exhibit the activity of betulinol, i.e., anti-cancer activity, at a desired site. Therefore, one of ordinary skill in the art would know how to use the compounds of claims 12-47.

Accordingly, the rejection of claims 1-47 for lack of enablement is improper and should be withdrawn.

The rejection of claims 3-6, 13, 15, 25, and 26 under 35 U.S.C. § 112, second paragraph, for indefiniteness is respectfully traversed in view of the above amendments and the following remarks. The rejection of claims 13, 15, 25, and 26 (applicants assume that the PTO is referring to claim 27) is obviated in view of the above amendments. With regard to the rejection of claims 3-6, it is the PTO's position that claim 3 (and its dependent claims 4-6) is indefinite as to the process steps, because if an alcohol is reacted with, e.g., acetonitrile, an ether will not be formed, regardless of the steps employed.

In contrast with the PTO's position, applicants have produced a diether in accordance with claims 3-6, as set forth in Example 3 of the Specification (at page 34, lines 2-6). In particular, betulinol was dissolved in acetonitrile in a betulinol-to-acetonitrile mole ratio of 1:40 (see Specification at page 34, lines 3-4). The solution was heated to 50°C and stirred for 20 minutes (see Specification at page 34, line 4). The crystalline residue, designated as "Cornelon", and having the following structure:



was washed with acetonitrile, filtered, and dried at 60°C (see Specification at page 34, lines 4-6). Cornelon was obtained in a 80-95% yield and was analyzed by HPLC (see Specification at page 34, line 6).

Accordingly, the rejection of claims 3-6, 13, 15, 25, and 26 for indefiniteness is improper and should be withdrawn.

In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: May 25, 2001

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below.	
May 25, 2001	Ruth R. Smith
Date	Ruth R. Smith

Appendix A

Version With Markings to Show Changes Made

In reference to the amendments made herein to claims 13, 15, 25, and 27, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In the Claims:

13. (Amended) A compound according to claim 12, wherein [-peptide-] "-peptide-" is a pentapeptide.

15. (Amended) A compound according to claim 12, wherein [-peptide-] "-peptide-" is a tetrapeptide.

25. (Amended) A method according to claims 23, wherein [-peptide-] "-peptide-" is a pentapeptide.

27. (Amended) A method according to claim 23, wherein [-peptide-] "-peptide-" is a tetrapeptide.